REMARKS

I. Status of the Claims and Amendments

Claims 18, 19, 22, 28, 29, 31, 32, 38, 39, 42, 53-56 and 65-67 are pending in the application. New claim 68 has been added. The claims stand rejected under 35 U.S.C. §112, 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Please note the amendment to claim 39. Previously, the term "antibody fragment" had been left out of the claim. This term has been reintroduced, though not through amendment as it was already part of the claim by virtue of the amendment filed on August 11, 2003.

II. Interview

Applicants wish to thank Examiner Helms for the courtesy of a telephonic interview held on October 12, 2004. Though agreement was not reached, applicants believe that the interview was helpful in clarifying the remaining issues.

III. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 22 and 42 stand rejected under the first paragraph of §112 as lacking an enabling disclosure. The examiner argues that claim 22 presents a situation where one CDR comprises a specific sequence, thereby placing additional constraints on the undefined structure of the remaining to CDRs in a given chain. Because these other CDRs are not specified, the examiner believes it would take undue experimentation to identify those sequences that would match with the specified sequence and retain 17-1A antigen binding. Applicants traverse.

What the examiner appears to overlook in the foregoing analysis is the existence of functional (*i.e.*, 17-1A antigen binding) antibodies. This is implicitly acknowledged by the fact that claims 18 and 21 are ***not*** rejected for enablement. Starting with such functional antibodies or fragments thereof, it would require only routine experimentation to modify two of the three CDRs of a given chain to obtain those which retained 17-1A binding activity, and comprised on fixed (*i.e.*, unchanged) CDR. Thus, the fact that claim 22 (and 42) specifies the particular sequence of a given CDR in the VH and VL chain, respectively, does not create an enablement hurdle for the skilled artisan.

Claims 18, 19, 22, 28, 29, 31, 32, 38, 39, 42, 53-56 and 65-67 are said to lack written description in the recitation of "as expressed on the surface of cells." Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite "tumor cells" as suggested by the examiner. Support for this amendment can be found on page 15, lines 28 to 30 of the corresponding WO 98/46645.

Reconsideration and withdrawal of both of these rejections is therefore respectfully requested.

IV. Rejections Under 35 U.S.C. §102 and §103 over Hoess

Claims 18 and 19 remain rejected over Hoess *et al.* ("Hoess"). As discussed previously by the examiner, Hoess teaches antibodies which bind human 17-1A antigen. However, the examiner is wrong in stating that Hoess describes antibodies that bind to ***native*** human 17-1A, and on this basis, applicant traverses. A review of Hoess reveals that the authors tested scFvs produced from a combinatorial library, having two different specificities – for 17-1A and LeY antigens. Although scFvs that bound 17-1A antigen were identified, these scFvs bound only to ***immobilized antigen*** and did not recognize tumor cells, and thus, this disclosure cannot

anticipate the presently claimed invention. In further support of this position, applicant points to de Kruif *et al.* (1995), at page 101, which states "None of the MoPhabs against ICAM-1 or δEGP-2 displayed binding to cells expressing these molecules ...." Thus, this reference teaches that these researchers failed to generate and isolate an anti-17-1A (there called EGP-2) antibody that recognized the native antigen.

Attached to the preceding response was the declaration of the inventor, Dr. Kufer, who was a coauthor on the Hoess *et al.* paper. Therein, Dr. Kufer stated that the human 17-1A antigen-specific antibody fragments described in the reference were only reactive with recombinant 17-1A antigen (EpCAM), and failed to bind human 17-1A antigen ***as expressed on the surface of cells (i.e., native 17-1A antigen)***. It also was noted that the significance of the de Kruif *et al.* (1995) paper was both (a) the well-known phenomenon that antibodies or fragments thereof isolated from combinatorial antibody libraries often bind to recombinant antigen, but do not necessarily bind to native antigens (*i.e.*, antigens expressed on the surface of cells), and (b) the failure of the authors to produce antibodies that react with native 17-1A antigen.

Moreover, it was pointed out that lines 1 to 10 from bottom of the Hoess *et al.* abstract stated: "To create multivalent antibodies displaying high affinities for cell surface antigens, scFv's can be fused .... The scFv4 recognizes specifically cancer cells overexpressing LeY compared to ...." No equivalent antibody construct specifically recognizing tumor cells expressing 17-1A antigen could be obtained, however. Thus, the cited abstract does not report on antibodies as now claimed.

Nonetheless, the examiner argues that Hoess *et al.* is enabling for preparing antibodies of the present invention. However, the examiner offers no basis for believing that this is so. In contrast, applicants have offered evidence (the Kufer Declaration) as to the failure of Hoess to

teach each element of the claimed invention – antibodies reacting with 17-1A antigen on the surface of tumor cells were not obtained. Moreover, applicants have also provided scientific reasoning as to why the prior art methods failed. The examiner has not rebutted either of these points.

Specifically addressing the issue of enablement, applicants acknowledge that the standard for determining whether a prior art reference is enabling is whether it would require undue experimentation for one of skill in the art to achieve that which is allegedly described. *Elan Pharmaceuticals v. Mayo Foundation*, 304 F.3d 1221 (Fed. Cir. 2002). However, in determining whether the experimentation is undue, one must look at a variety of factors, for example, as set out in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Here, two critical factors mitigate ***against*** a finding that cited reference is enabled – the lack of a working example showing the present invention (an antibody that binds to the 17-1A antigen on the surface of tumor cells) and a valid reason to doubt whether the technology disclosed in the reference would ***ever*** succeed. Thus, even if the examiner had created a *prima facie* case that Hoess was enabled, which applicants deny, the evidence now of record would have proven otherwise.

And because Hoess is not enabling as a novelty-defeating reference, the parallel obviousness rejection under §103 is similarly defective. Therefore, applicants respectfully submit that Hoess cannot anticipate or obviate the present invention, and reconsideration and withdrawal of the rejection is respectfully requested.

V. Rejection Under 35 U.S.C. §103

Claims 18, 19, 28-31, 38, 39, 53-55, 65 and 67 remain rejected as obvious over the '584 patent in view of Gottlinger. Applicants once again traverse.

The antibodies of the invention are characterized as being only low or not at all immunogenic in humans. This is achieved by the use of unprimed mature human B-lymphcytes as the source for the VH chain. The use of such cells results in the absence of amino acid exchanges from somatic mutations in at least the VH regions, thereby avoiding immune responses. This is exemplified by VH-regions D4.5 (FIG. 7) and D7.2 (FIG. 8) of the invention which can be clearly assigned to the germline sequences of mature unprimed human B cells (see the attached sequence alignments of Annexes 1 and 2 of the reply to Written Opinion).

In contrast, the human antibodies generated in transgenic mice as described in the '584 patent undergo affinity maturation via somatic mutation (see, for example, the attached Figure 12A of the '584 patent, showing a DNA sequence alignment of the somatically mutated heavy chain of anti tetanus toxin monoclonal antibody D5.1.4 and germline VH6). That the antibodies generated by the method of the '584 patent are derived from somatically mutated sequences is underlined by a publication by Mendez *et al.* (1997), which originates from Abgenix, the assignee of the '584 patent. For example, Figure 6 on page 153 of Mendez *et al.* shows somatic hypermutation in, *inter alia*, VH chains of xenomouse-derived fully human Mabs. Moreover, the authors on page 154, left column, 2nd paragraph, lines 26 to 30 state that:

> These high affinities combined with the extensive amino acid substitution as a result of somatic mutation in the V genes confirms that the mechanism of affinity maturation is intact in xenomouse II and comparable to that of wild-type mice.

In addition, human antibodies generated according to the transgenic mouse approach described in the '584 patent are at risk of forming immunogenic epitopes that may induce an undesired immune response in human, without being recognized as a foreign antigen resulting in subsequent elimination. This is because these antibodies have never had to stand the

surveillance of the human immune system. Particularly, these antibodies have been selected for being tolerated by the murine but not the human immune system (see the description of the present application on page 4, first paragraph, of the corresponding WO 98/46645).

In summary, the antibodies of the invention exhibit a superior immunologic profile (low antigenicity) as compared to the antibodies described in the '584 patent, arising from:

- avoiding somatic mutations at least within the VH-region
- prior *in vivo* exposure of the V-regions of the antibodies of the invention resulting in a preselection of V-regions that are well tolerated by the human immune system

The '584 patent fails to provide any direction to use of unprimed mature human B-lymphocytes. Thus, a person skilled in the art would not glean from the teachings of the '584 patent application the use of germline VH sequences, *i.e.*, non-mutated sequences. Accordingly, the teachings of the '584 patent do not enable the production of low or non-immunogenic antibodies, nor was there a reasonable expectation of success for the skilled person to obtain such antibodies. This is true simply because the '584 patent is completely silent about an appropriate B cell source, *i.e.*, unprimed mature human B lymphocytes which allow the generation of germline sequences-derived antibodies according to the invention.

The above-mentioned defects in the '584 patent are not cured by Göttlinger *et al.* This publication is completely silent about anti-17-1A human antibodies which are low or not immunogenic in humans. There is no mention in Göttlinger *et al.* of using unprimed mature human B-lymphocytes. Thus, by following the teaching of the '584 patent in combination with Göttlinger *et al.*, enablement of the claimed invention still is lacking, and as well, a person

skilled in the art still would not have had any reasonable expectation of success to obtain the claimed antibodies.

In sum, the cited art fails to teach each element of the claimed invention - low or non-immunogenic antibodies to 17-1A – and it fails to enable this given the absence of any teaching with respect to the use of germline antibody genes. As such, the rejection is improper; reconsideration and withdrawal thereof is respectfully requested.

VI. Conclusion

All claims are believed to be in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Helms have any questions regarding this response, a telephone call to the undersigned is invited. Please date stamp and return the enclosed postcard as evidence of receipt.

Respectfully submitted,

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